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on Drugs and Therapeutics

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CHLOROMYCETIN

Chloramphenicol (Chloromycetin--Parke-Davis) is one of many drugs whose value sometimes justifies their use despite the risk of severe toxic or side effects. Nevertheless, it should be used with great caution since serious and even fatal blood dyscrasias have followed short-term as well as prolonged administration.

It is true that the number of cases of Chloromycetin-induced agranulocytosis reported in the American literature has greatly decreased, but this is only because American hematologists have generally accepted the fact that this antibiotic causes aplastic anemia; apparently they consider it hardly worthwhile to report another case or two. Actually, there has been a steady increase during the past few years in the number of cases of aplastic anemia associated with Chloromycetin administration, an increase presumably resulting from freer use of the drug.

WHERE CHLOROMYCETIN SHOULD BE USED - Despite the hazard, Chloromycetin remains the drug of choice in severe Salmonella infections and in severe Hemophilus-influenzae meningitis, croup and pneumonia. Although it is a broad-spectrum antibiotic, effective against many gram-positive and gram-negative organisms as well as against many resistant staphylococci, it should not be used where penicillin, the tetracyclines or erythromycin are effective. It may be useful, despite the risk, in the hospital management of resistant staphylococcus and urinary-tract organisms.

It cannot be too strongly emphasized that Chloromycetin therapy requires regular and frequent blood studies, especially with prolonged therapy. At the first evidence of hemotoxic effect, the antibiotic should be promptly discontinued.

ORAL VS. PARENTERAL ADMINISTRATION - When Chloromycetin is used, oral administration is almost always preferable to parenteral. In general parenteral administration is indicated only where the patient is unable to take it by mouth, or where oral ingestion results in gastritis or diarrhea. When it is taken orally, it is rapidly absorbed, it consistently produces adequate blood levels, and it diffuses well throughout the body and into the spinal fluid, the biliary tract and other body fluids.

Intramuscular administration does not give significantly more rapid absorption than oral, nor does it produce significantly higher blood levels (In some

patients, intramuscular administration may be relatively slow in producing satisfactory blood levels because of the variability of absorption from intramuscular sites.) A new parenteral form of Chloromycetin (the acid succinate) will soon be marketed by Parke-Davis. While it presumably has the advantage of being less irritating than the older form, when it is administered intramuscularly it does not give higher blood levels than oral doses (Antibiotics Annual, 1957-58, p. 798). Indications for intravenous use of Chloromycetin are infrequent.

Not to be overlooked is the fact that parenteral in place of oral administration subjects the patient to unnecessary discomfort, and there is the added factor of the higher cost of Chloromycetin in the parenteral forms. Where 250-mg. capsules cost the patient about 50¢ each, the cost of 250 mg. as prepared for intramuscular injection is about $1, and for intravenous injection, about $1.75. The pediatric oral suspension (Palmitate) costs about $4 for a 60-cc. vial containing fifteen 125-mg. doses.

LERITINE

Anileridine hydrochloride (Leritine-Merck), a derivative of meperidine (Demerol-Winthrop), has been used long enough now to establish the fact that it is a valuable analgesic-narcotic. Parenterally, 40 mg. of Leritine give approximately the same analgesic effect as 100 mg. of Demerol. Anorexia and most other side effects appear to be similar when the two drugs are given in equipotent analgesic doses. Both drugs probably cause respiratory depression of about the same severity and duration. Clinical reports are conflicting about the sedative effect of Leritine. Whether it has more or less sedative effect than equal analgesic doses of Demerol remains to be established; in one controlled study of sedative effect, relatively more Leritine was required than would have been anticipated from the accepted 4:10 analgesic ratio.

EUPHORIC EFFECT - In Roswell Park Memorial Institute, Buffalo, where the drug has been compared with other analgesics in treating the severe pain of advanced cancer, Leritine has been found to produce considerable euphoria when first administered. After about 10 days, however, as tolerance to the drug develops, the euphoric effect is lost.

Like Demerol, Leritine can be given orally as well as parenterally. The recommended adult oral dosage is 25 mg. for mild pain, 50 mg. for moderate pain, and 50 to 75 mg. for severe pain, although controlled experiments on the relative efficacy of oral and parenteral administration have not been reported. It is said to maintain effective analgesia for as much as four hours under favorable conditions, though patients with severe pain may require medication every three hours.

Leritine is a narcotic, and is definitely addicting. A recent clinical study which suggested a lack of addicting properties did not evaluate this feature critically. It will be recalled that Demerol was at first mistakenly considered to be free of addicting properties. As with other narcotics, the respiratory depression caused by Leritine can be reversed by administration of nalorphine (Nalline-Merck) or levallorphan (Lorfan-Roche). Lorfan has the advantage, at least for

hospital use, that it is not a narcotic and therefore can be kept unlocked in open stock.

On the whole, the differences between Leritine and Demerol are slight and, for most patients, of no significance. For equal analgesic doses, the list price of Leritine is about 20 per cent less than that of Demerol.

ZACTANE AND ZACTIRIN

Ethoheptazine (Zactane-Wyeth) is a relatively new oral analgesic drug which appears to offer no problem of addiction or drug tolerance. Although it is structurally related to meperidine (Demerol), its analgesic effects are quite mild. In the recommended dose of 75 mg. it is not likely to be more effective than ordinary doses of aspirin, though available clinical studies do not permit reliable comparison of the two drugs. Side effects are probably not a serious problem; it is, however, too early for final judgment on the manufacturer's claim that they "are infrequent and minor - as nausea, epigastric distress and dizziness."

Zactane is now promoted chiefly in a combination consisting of 75 mg. of ethoheptazine and 5 grains of aspirin. The combination, Zactirin, is claimed to offer the analgesic equivalent of 1/2 grain of codeine plus 10 grains of aspirin "without the undesirable side-effects or addiction liability of codeine." Since the addiction liability of codeine is very slight and of no significance with most patients seen in office practice, and since the side effects of codeine are rarely serious, the advantage of routinely substituting a new and relatively untried drug such as Zactirin is questionable. Nevertheless, a new drug is sometimes psychologically desirable for patients with long-standing ailments. Zactirin should be used, however, with the awareness that it is a drug whose effectiveness and side effects remain to be fully appraised. Each tablet of Zactirin costs the patient about the same as a half-grain tablet of codeine (about 7¢).

ORAL COLD REMEDIES

What, if anything, can the advertised oral cold and sinus remedies accomplish? This question arises more and more frequently as an increasing number and variety of shot-gun remedies are marketed, many by ethical drug houses - preparations such as Sinutab, Tussagesic, Dristan, Rynatan, Triaminicin, Duadacin, Romilar CF, Nolamine, Coricidin and others. The claims for Sinutab are typical: "Resolves sinus headache; now - all cold symptoms can be controlled."

THEIR INGREDIENTS - Almost all of the preparations contain one or two antihistamines and a vasoconstrictor, usually neosynephrine. Many contain analgesic and antipyretic compounds, a few contain cough inhibitors, caffeine and Vitamin C. One ethical cold remedy, Madricidin (Roche), contains a long-acting sulfonamide in addition to other standard cold-remedy ingredients. Others contain antibiotics such as penicillin (V-Kor--Lilly, for example) or tetracycline (Achrocidin-Lederle, for example). It need hardly be said that none of the preparations will prevent, abort or cure a cold. All of the preparations, however,

contain ingredients having some value for the relief of particular cold symptoms. If there is stuffiness the vasoconstrictors may, of course, be helpful; if there is grippe with pain and fever the analgesic-antipyretic compounds may give relief, though it is doubtful that they offer any advantage over plain aspirin. But there is less agreement about some of the other ingredients.

Cold remedies containing sulfa or antibiotics should never be prescribed since they introduce the risk of sensitization and severe allergic reactions for a self-limited mild infection, and since there is no proof that either sulfa or an antibiotic can prevent bacterial complications of upper respiratory infections.

THE ANTIHISTAMINES - Soon after the antihistamines appeared, it was claimed that they could reduce the severity and duration of upper respiratory infections. Many clinical reports followed, some confirming, some denying the claim. The perspective provided by time and experience shows that this much is true: in some patients antihistamines do reduce rhinorrhea and sneezing. In many patients, perhaps most, they are of no value. Despite the presence of ephedrine derivatives in most of the preparations, the antihistamines will cause occasional drowsiness. Some patients are convinced that the duration of their colds is shortened by antihistamines. The well-known variability of both duration and severity of respiratory infections, as well as the responsiveness of colds to placebo therapy, make the patients' conviction easy to understand, but it has never proved itself against well-controlled, double-blind tests.

SINUS TREATMENT - Claims concerning sinus drainage are made for many cold remedies. While some patients with colds feel so-called "sinus discomfort," the pain is often a reflex from inflammatory irritation of the nasal mucosa. Whether it is that or, in fact, acute catarrhal sinusitis, it will generally resolve spontaneously without any therapy. Acute suppurative sinusitis, of course, requires effective chemotherapy or antibiotic treatment, in addition to measures to promote drainage.

As for Vitamin C, there is no evidence that it is of the slightest value in preventing or relieving colds. If the diet is deficient in this vitamin, a cold remedy is hardly the best treatment for it. A further word about vasoconstrictors: the sympathomimetic drugs (such as neosynephrine) contained in many of these preparations may offer advantages over intranasal medication with such drugs in providing longer, more uniform vasoconstricting action on the mucous membrane of the nose without the rebound reaction characteristic of intranasal medication. (For the vasoconstricting effect alone, phenylpropanolamine or ephedrine, about 25 mg., may be prescribed.) But it should also be remembered that many patients are sensitive to sympathomimetic drugs and experience palpitation and nervousness even after small doses.

(Comment on "Oral Cold Remedies" by a Medical Letter consultant: "The criticism is a little too mild. I view with alarm this excursion of pharmaceutical houses into the promotion of these shot-gun mixtures. Their promotional approach is substantially that of the Dristan and Five-Way Cold Remedy group. The only difference is that their target is the physician.")

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